of these claims in another application. New claim 17, based on original claim 9, has been added. Applicants have amended claims 7, 9, 11, and 12 to independent form so that they no longer depend from non-elected claims. Applicants have also amended claims 7, 9, 11, 12, and 14 to more distinctly define the claimed subject matter. A version of the pending claims marked to show these changes is submitted with this Amendment. The amendments and new claim 17 are fully supported by the specification and claims as filed. No new matter has been added. Upon entry of these amendments claims 7, 9, 11, 12, 14, and 17 are pending in the application.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 7, 9, 11, 12, and 14 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which is not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner contends that the specification lacks working examples and does not teach modes of adminstration of BMP-9 to a patient. In addition, the Examiner contends that the fields of protein-based pharmaceuticals and treatment of neurodegenerative diseases are unpredictable and the specification does not provide the specific guidance needed to practice the invention. Applicants respectfully traverse this rejection.

Applicants would like to address the intended scope of the claimed invention. The claimed invention comprises administering BMP-9 to a patient to:

(1) differentiate cholinergic neurons (see Example IV and page 2, lines 7-8);

(2) treat degenerating and/or malfunctioning cholinergic neurons (see Example VII, page 3, lines 15-22, and page 6, lines 12-15);

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(3) upregulate choline acetyltransferase (see Examples II, V, and VI, Fig. 1, and page 6, lines 7-11);

(4) upregulate vesicular acetylcholine transporter (see Examples III, V, and VI and Fig. 1); and

(5) treat degenerating motor neurons (see page 2, lines 19-21).

These claims all refer to the upregulation of the cholinergic phenotype in neurons. These claims are wholly supported and enabled by the specification. Sufficient working examples, modes of delivery and enabling disclosures are present throughout the specification, and the Applicants have provided the skilled artisan with all the necessary information for practicing the claimed invention, that is, inducing the cholinergic phenotype in neurons.

The Examiner contends that the specification does not provide working examples with regard to treatment of a diseased animal. The examples of the instant specification disclose the activity of BMP-9 in cultured mouse neurons and in whole mouse embryos (see Example I). It is well within the skill of one in the art to extrapolate the results taught in the specification to adult animals. Administration of protein compounds to adult animals and humans requires nothing more than the routine determination of the appropriate dosage. Therefore, the working examples present in the specification support the claimed invention of upregulating the cholinergic phenotype by administration of BMP-9.

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The Examiner contends that the specification does not provide specific guidance regarding a mode of administration. Applicants point out to the Examiner parts of the specification on page 3, lines 23-27, page 6, line 23 to page 7, line 3, and page 8, line 4 to pg 9, line 22, all devoted exclusively to disclosure of modes for administration of

BMP-9 to the brain or motor neurons. With this disclosure, a skilled artisan can apply the vast realm of knowledge on the specifics of protein therapeutics to the delivery of BMP-9. Delivery of therapeutic proteins is not a novel concept, and it is not the purpose of a patent specification to restate what is well known to those of skill in the art. See the cited references below for more evidence that the skill of protein delivery for therapeutic purposes was readily available to those skilled in the art.

The Examiner further states that the specification fails to provide an enabling disclosure for the treatment of patients because in the absence of specific guidance, protein therapy is unpredictable. While addressing this issue, however, the Examiner repeatedly refers to difficulties known to exist in the treatment of Alzheimer's disease. Applicants respectfully submit that the claims do not require treatment of Alzheimer's disease. The claimed invention requires only upregulation of the cholinergic phenotype in a patient by administering BMP-9. In Examples II-VII, Applicants have demonstrated that treatment of neurons with BMP-9 will induce the cholinergic phenotype. The predictability of the claimed effects occurring during treatment with BMP-9 (such as upregulation of choline acetyltransferase genes) cannot be compared to the predictability of curing Alzheimer's disease, as the Examiner seems to do. Discussed below are three references, indicating the skill in the art as of the filing date of the instant application. These references demonstrate that protein therapy for the upregulation of the cholinergic phenotype was well within the skill of one in the art.

As an enabling example, Barnes et al., Neuroscience 2000 99(1)17-23 (copy enclosed), discloses the treatment of aging rats with an inhibitor of acetylcholinesterase (AchE). This inhibitor induces the cholinergic phenotype in much the same way that

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BMP-9 does, by increasing acetylcholine levels. Treatment of old rats with AchE inhibitors increased the maintenance of synaptic plasticity, a marker of neurodegenerative disease. Barnes et al. demonstrates that it was within the skill of one in the art to use compounds proven functional in cell culture to treat disease in mammals.

Walton et al., Pharmaceutical Research 1998 15(3):377-385 (copy enclosed), discloses the delivery of glial cell line-derived neurotrophic factor (GNDF) as a therapeutic agent for neurodegenerative disease. Additionally, Haller et al., Molecular Neurobiology 1999 19(1):43-59 (copy enclosed), discloses many methods for the delivery of proteins to the brain for therapeutic purposes. In light of these two references, Applicants submit that it was within the skill of one in the art as of the filing date of this application to administer proteins to treat neurodegeneration.

The Examiner perceives the invention to solely pertain to the treatment of Alzheimer's disease. Applicants submit that this interpretation improperly incorporates limitations not found in the claims. The specification provides sufficient guidance to those skilled in the art to treat degenerating neurons in a patient with BMP-9. Thus, the specification does inform skilled artisans how to practice the claimed invention, that is, how to differentiate cholinergic neurons, upregulate choline acetyltransferase and vesicular acetylcholine transporter levels, and treat degenerating neurons. One skilled in the art can use the disclosure of BMP-9 and methods of administering BMP-9 to produce the claimed effects with little to no additional experimentation.

Therefore, Applicants respectfully request that the rejections to claims 7, 9, 11, 12, and 14 under 35 U.S.C. § 112, first paragraph be withdrawn.

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Rejection under 35 U.S.C. § 112, second paragraph

Claims 7, 9, 11, 12, and 14 are rejected as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention.

The Examiner states that claims 7, 9, 11, and 12 are indefinite because they depend from claims directed to non-elected inventions. Claims 7, 9, 11, and 12, as amended, are no longer dependent on non-elected claims, removing the grounds for this rejection.

Claim 7 is allegedly indefinite in its recitation of "differentiating cholinergic neurons because it is unclear what the cholinergic neurons differentiate into. Claim 7, as amended, makes it clear that progenitor cells differentiate into cholinergic neurons. The claim does not require cholinergic neurons themselves to differentiate, thus removing the grounds for this rejection.

Claim 11 is allegedly unclear as the result of grammatical error. Claim 11, as amended, is no longer grammatically incorrect, thus removing the grounds for this rejection.

Claims 7, 9, 11, 12, and 14 are considered indefinite by the Examiner because they do not contain conclusory statements stating that the administration of BMP-9 will have the desired effect stated in the preamble of the claims. Applicants do not agree that such statements are necessary to render the claims definite under 35 U.S.C. § 112, second paragraph. However, in an effort to further prosecution, claims 7, 9, 11, 12, and 14 are amended to include a requirement that the BMP-9 composition administered performs the function stated in the preamble. These amendments overcome the rejections of claims 7, 9, 11, 12, and 14 under 35 U.S.C. § 112, second paragraph.

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In view of the foregoing amendments and remarks, Applicants respectfully requests the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any required fee to deposit account 06-0916.

Respectfully submitted,

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Dated: January 2, 2003

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Pending Claims with Markings to Show Changes

7. (Amended) A method for differentiating progenitor cells into cholinergic neurons in a patient in need of same comprising administering to said patient a pharmaceutical composition comprising an amount of BMP-9 in a pharmaceutically acceptable vehicle sufficient to induce differentiation of progenitor cells into cholinergic neurons [~~an effective amount of the composition of claim 4~~].

9. (Amended) A method for treating degenerating [~~and/or malfunctioning~~] cholinergic neurons in a patient in need of same comprising administering to said patient a pharmaceutical composition comprising an amount of BMP-9 in a pharmaceutically acceptable vehicle sufficient to induce differentiation of progenitor cells into cholinergic neurons [~~an effective amount of the composition of claim 3~~].

11. (Amended) A method for upregulating the genes for choline acetyltransferase in a patient in need of same [~~some~~] comprising administering a pharmaceutical composition comprising an amount of a BMP-9 protein in a pharmaceutically acceptable vehicle sufficient to upregulate the genes for choline acetyltransferase in [~~composition of claim 5 to~~] said patient.

12. (Amended) A method for upregulating vesicular acetylcholine transporter in a patient in need of same comprising administering a pharmaceutical composition comprising an amount of a BMP-9 protein in a pharmaceutically acceptable

vehicle sufficient to upregulate vesicular acetylcholine transporter in [~~composition of claim 6 to~~] said patient.

14. (Amended) A method for treating degenerating motor neurons in a patient in need of same comprising administering to said patient an [~~effective~~] amount of a BMP-9 composition sufficient to prevent degeneration of motor neurons in said patient.

17. (New) A method for treating malfunctioning cholinergic neurons in a patient in need of same comprising administering to said patient a pharmaceutical composition comprising an amount of BMP-9 in a pharmaceutically acceptable vehicle sufficient to induce differentiation of progenitor cells into cholinergic neurons.